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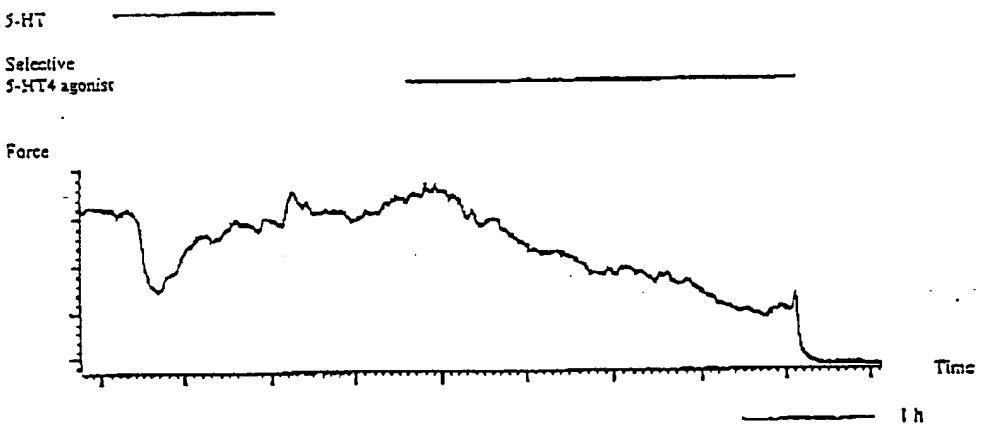


(57) Abstract

The present invention relates to a compound having agonist activity to the 5-HT_4 receptor for use as a medicament and to the use of said compounds in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchoconstriction of a human or animal body, as well as methods of treatment, wherein said compounds are administered. The present invention also relates to a compound having antagonist activity to the 5-HT_{2a} receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchoconstriction of a human or animal body, as well as methods of treatment, wherein said compounds are administered.

MEDICAMENT

Field of the Invention

The present invention relates to a compound having agonist activity to the 5-HT_4 receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compound is administered. The present invention also relates to a compound having antagonist activity to the 5-HT_{2a} receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compound is administered.

Background of the Invention

Receptors of the 5-HT (serotonin; 3-(β-aminoethyl)-5-hydroxyindole) type are well known and occur throughout the body, e.g. in the airways, and their relevance has mainly been reported in conjunction with treatment of CNS, muscle and gastric disorders, as disclosed in e.g. WO 98/18458 and US 5 246 935. In such treatments, compounds having agonist activity to a 5-HT_1 type receptor are often used. As examples of other 5-HT receptors, mention can be made of receptors of the 5-HT_2, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 type. For a recent review of 5-HT receptors, see Gerhardt, C.C., van Heerikhuizen, H., *Eur. J. Pharm.*, 334, 1-23 (1997), which is incorporated herein by reference.

Receptors of the 5-HT_2 type are also well known, e.g. through US 5 869 497, US 5 705 519 and US 5 246 935. The relevance of receptors of the 5-HT_2 type has been reported in conjunction with *e.g.* CNS and neuronal disorders. Such disorders are often treated with compounds having antagonist activity to a receptor of the 5-HT_{2a},

5-HT_{2B} or 5-HT_{2C} type. Examples of such compounds are ritanserin and naftidrofuryl. A review of typical agonists and antagonists of various 5-HT receptors is disclosed in R.A. Glennon, Neuroscience and Biobehavioral Reviews, 14, 35-47 (1990), the whole content of which is incorporated herein by reference.

SU 1 701 320 A1 discloses the use of serotonin for treatment of acute asthma attacks. This reference does not suggest any receptor mechanism for serotonin, which is a compound with both a contracting and a relaxing effect on the airways, as is further discussed herein below.

In the RBI Handbook or Receptor Classification and Signal Transduction, 3rd Edition, 1998, RBI, One Strathmore Road, Natick, MA 01760-2447, USA, Editor: Keith J. Watling are compounds having agonist or antagonist activity to various receptors disclosed.

Disclosure of the Invention

The present invention is based on the novel finding that certain 5-HT receptors are of utmost importance in regulating bronchocontraction. In summary, it is disclosed herein that compounds having agonist activity to the 5-HT_4 receptor bring about a bronchorelaxing action upon administration thereof, and are therefore suitable as agents for treatment of bronchocontraction disorders. It is also disclosed herein that compounds having antagonist activity to the 5-HT_2, especially 5-HT_{2a}, receptor, are suitable agents in the treatment of bronchocontraction disorders. Methods for treatment of bronchocontraction disorders are also disclosed.

As used herein, the expression bronchocontraction disorder refers to an abnormal increase of the force development of the smooth muscle, resulting in a reduced diameter in some or all of the airways of the lungs and/or the extrapulmonary airways. Said expression also refers to reduction of airflow caused by swelling, oedema,

plasma extravasation or mucous secretion caused by *e.g.* asthma or any other disorder related thereto.

Accordingly, the present invention relates, in one of its aspects, to a compound having agonist activity to the 5-HT_4 receptor for use as a medicament. In another aspect it relates to use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma.

In a preferred embodiment, the invention relates to the use of a compound having agonist activity to the 5-HT_4 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said agonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

The present invention also relates, in another aspect, to a compound having antagonist activity to the 5-HT_{2a} receptor for use as a medicament. In another aspect it relates to use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma.

In a preferred embodiment, the invention relates to the use of a compound having antagonist activity to a 5-HT_{2a} receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said antagonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

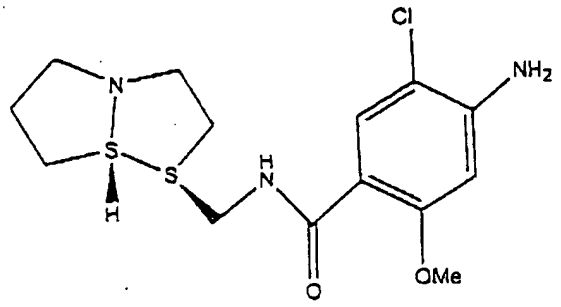
Said bronchocontraction may also occur in conjunction with such disorders as *e.g.* emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depres-

sion, anorectic or bulimic eating disorders, anxiety or various psychotic conditions, including schizophrenia.

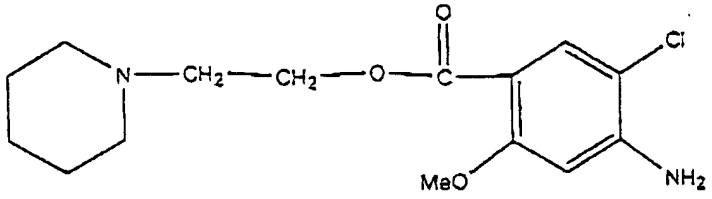
The present invention also relates to the use of a compound having antagonist activity to a 5-HT_{2a} receptor in combination with a compound having agonist activity to the 5-HT_4 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction. In a preferred embodiment said compound having agonist activity is serotonin or a derivative thereof having agonist activity to the 5-HT_4 receptor. This combination of the 5-HT_{2a} receptor antagonist and the agonist increases the serotonin transmission in the body, particularly in the presence of a serotonin uptake inhibitor (SRI). Further, the compounds having agonist activity to the 5-HT_4 receptor to be used according to the present invention are also useful in the present combination embodiment. In particular, said medicament is intended for treatment of asthma and disorders related thereto.

According to the present invention several known substances are, surprisingly, able to stimulate the 5-HT_4 receptor, without activating the contracting 5-HT_{2a} receptor, thereby generating a relaxing effect on the bronchocontraction. Such agonist compounds are selected from the group comprising the substances SC 53116, ML 10302, RS 67506 and BIMU 6, which are defined below, as well as the more unspecific 5-carboxamidotryptamine, and derivatives and pharmaceutically acceptable salts thereof having the same or essentially the same relaxation effect.

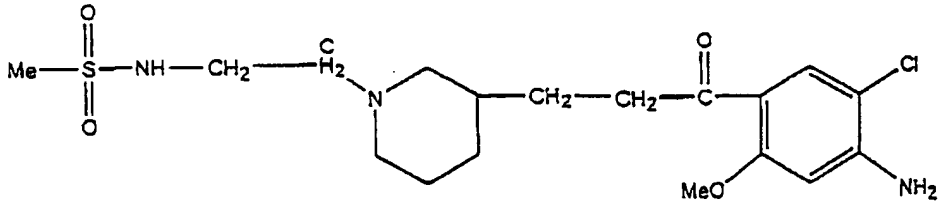
The invention also relates to the use of one or more of the above-mentioned agonist compounds: SC 53116, i.e. 4-amino-5-chloro-N-[[1S, 7aS)-hexahydro-1H-pyrrolizin-1-yl]methyl]-2-methoxy-benzamide, having the structural formula:



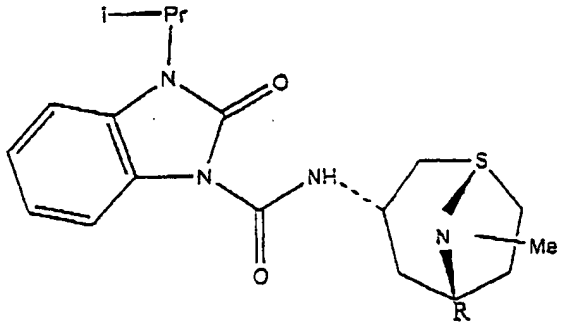
ML 10302, i.e. 4-amino-5-chloro-2-methoxy-benzoic acid-2-(1-piperidinyl)ethylester, having the structural formula:



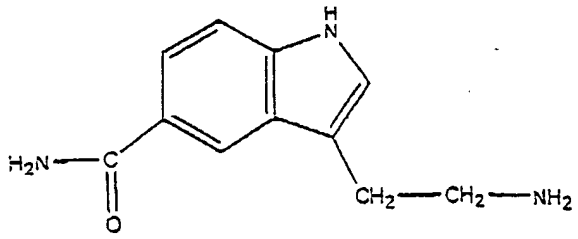
RS 67506, i.e. N-[2-[4-[3-(4-amino-5-chloro-2-methoxyphenyl)-3-oxopropyl]-1-piperidinyl]ethyl]-methanesulfonamide monohydrochloride, having the structural formula:



BIMU 8, i.e. 2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide monohydrochloride, having the structural formula:



5-carboxamidotryptamine, having the structural formula:

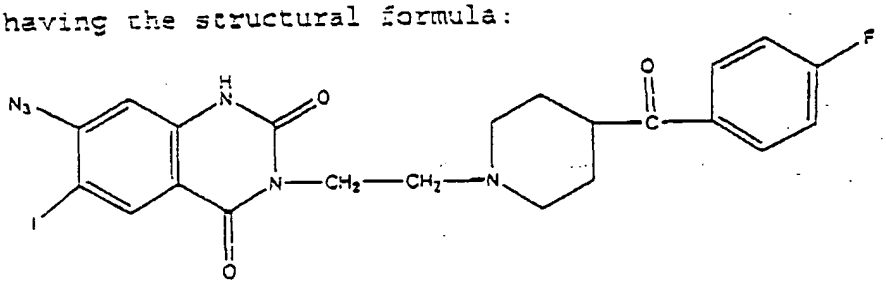


BIMU 1, BIMU 8, BRL 24924, Cisapride, DAU 6236, 5-hydroxy-N,N-dimetyltryptamin, ML-1035, ML10302, 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877, Renzapride, RS 17017, RS 56532, RS 57639, RS 67333, RS 67506, RS 67532, SB 204070, SB 205149, SC-53116, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, YM-47813, YM-53389, YM-09151, Zacopride, Zelmac and derivatives and pharmaceutically acceptable salts thereof having essentially the same relaxing effect, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said agonist

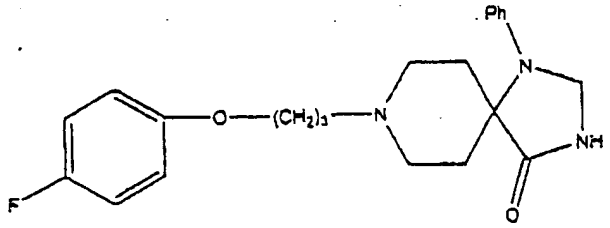
has the capacity of reducing the bronchocontraction by at least 30%, preferably at least 60%, most preferably at least 90%.

According to the present invention several known antagonist compounds are, surprisingly, able to influence the 5-HT_{2a} receptor, thereby generating a contraction reducing effect, i.e. a relaxation effect, and are selected from a group comprising ketanserin, AMI-193 or MDL 100 907, and derivatives and pharmaceutically acceptable salts thereof having the same or essentially the same contraction reducing effect.

Thus, the invention also relates to the use of one or more of the above-mentioned compounds, namely: ketanserin, i.e. 7-azido-3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-6-iodo-2,4(1H, 3H)-Quinazolinedione, having the structural formula:



AMI-193, i.e. 8-[3-(4-fluorophenoxy)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, having the structural formula:



and ALEPH-2, Amperozide, amesergide, Aryloxyalkylimidazolines, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-6-fluoroindolin-2(1H)-one, CGS 18102A, Clonidine, Cyproheptadine, Deramciclane, Desmethyl-WAY 100635, dotarizine, DV 7028, Elymo-

clavine, Fananserin, 8-[3-(4-fluorobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]de can-4-one, FG5893 hydrochloride, FG5974, FG5983, Hexahydrocarbazoles, (3H)WAY 100635, ICI169,369, 8-[3-(4-iodobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]deca n-4-one, Ketanserin, LEK-8804, LSD, LU 111995, (S,S) -LY-53,857, (R,S)-LY-53,857, (S,R)-LY-53,857, (R,R)-LY-53,857, LY-53,857 free base, LY 215840, MDL-11,939, MDL 28133A, MDL 100,151, MDL 100,907, mesulergine, Metergoline, 1-3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl indolin-2(1H)-one, methysergide, Mianserin, NE-100, Nefazodone, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, NRA0045, Olanzapine, Ondansetron, 1-(2-pyrimidinyl)piperazine derivatives, Pizotifen, raclopride, Roxindole, Risperidone, Ritanserin, RP62203, sarpogrelate and its active metabolite (M-1), serotonin reuptake inhibitors like fluoxetine, YM 992, medifoxamine, cericlamine, imipramine, iprindole, BIMT 17, citalopram, paroxetine, sertraline, fluvoxamine spiro indoles N-substituted with a 3-(dimethylamino)-propyl chain Spiperone, SR 46349B, WAY 100635, WY-50,324, MDL 100,907, and derivatives and pharmaceutically acceptable salts thereof having essentially the same contraction reducing effect, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said antagonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

Ketanserin is excluded from the embodiment concerning the 5-HT_{2a} receptor antagonist compound for use as a medicament.

The present invention also relates to a method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of the

compound according to the present invention having agonist activity to the 5-HT_4 receptor. Preferably, said method relates to the treatment of asthma and disorders related thereto.

The present invention also relates to a method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to the present invention having antagonist activity to a 5-HT_{2a} receptor. Preferably, said method relates to treatment of asthma and disorders related thereto.

Further, the present invention relates to a method for treatment of disorders involving bronchocontraction, wherein the above-mentioned combination of agonist(s) and antagonist(s) is administered.

The expression "has the capacity of reducing the pathological bronchocontraction by at least ....%" used throughout the present patent application means that the compound in question reduces the contraction in the airways caused (1) either by the underlying disease (asthma etc) or (2) by the administration of 5-HT or other substances with 5-HT2a-activating properties. The level of contraction in the airways can, for instance, be determined by spirometric measurements of the Forced Expiratory Volume (FEV1), compared to the normal value for healthy people. Alternatively, the expiratory capacity for a patient can be compared to his own FEV1 during periods of relatively little obstructive problems.

As appears from Fig. 1, the contractile component often manifests itself as a reduction or a complete elimination of the 5-HT induced relaxation, rather than in an increase of force from the control (pre-exposure) level. In the case of "specific" agonists to the 5-HT_4 receptor, this sustained relaxing effect is achieved because the contractile 5-HT_{2a} receptor is not affected; only the relaxing 5-HT_4 receptor is activated. In the

case of antagonists to the 5-HT_{2a} receptor, this effect is achieved due to direct blocking of the 5-HT_{2a} receptor, whereby the unspecific agonists to the 5-HT_4 receptor, such as 5-HT, can act without also causing contraction by the 5-HT_{2a} receptor.

It should be noted that the medicament prepared according to present invention in each embodiment may optionally include two or more of the above outlined compounds.

Further, in the embodiment when the compound having 5-HT_{2a} antagonist activity is administered, optionally together with complementary serotonin or derivatives thereof, a serotonin uptake inhibitor can be added with a view to amplifying the relaxing effect.

The typical daily dose of the medicament prepared according to the invention varies within a wide range and will depend on various factors such as the individual requirement of each patient and the route of administration.

Said medicament may be prepared as a composition adapted either for administration via the respiratory tract or for oral, intravenous, topical, intraperitoneal or subcutaneous administration, in association with one or more pharmaceutically acceptable carriers, diluents or adjuvants that are well known in the art.

Moreover, said medicament is preferably administered via the respiratory tract in the form of *e.g.* an aerosol or an air-suspended fine powder. However, in some cases a useful alternative to administration via the respiratory tract may be oral, topical, parenteral, subcutaneous, transdermal or rectal administration, wherein *e.g.* tablets, capsules, powders, microparticles, granules, syrups, suspensions, solutions, transdermal patches or suppositories are utilized.

Brief Description of the Drawing

Fig. 1 depicts the effects of 5-HT and selective 5-HT_4 agonists on the spontaneous tone in human in vitro

preparations. Note that 5-HT only gives a transient relaxation, while selective 5-HT_4 agonists give a strong sustained relaxing effect.

Detailed Description

The subject-matter of the present invention was inter alia deduced from animal experiments, where a specific behavior of the airway smooth muscle called "spontaneous tone" was examined. The spontaneous tone, which involves a spontaneous continuous contraction in the airway smooth muscle, was studied due to a suspicion that defective regulation of the spontaneous tone could be an important cause of the bronchoconstriction observed in asthmatic patients.

The examinations of the spontaneous tone were performed in accordance with the methods disclosed in the thesis "*Regulation of spontaneous tone in guinea pig trachea*" by S.Skogvall, Department of Physiological Sciences, Lund University, 1999, which is incorporated herein by reference. As evidenced by these examinations, the airways normally display a highly regular type of oscillating tone if exposed to physiological conditions, and the oscillating tone can be reversibly affected by administration of various substances. When the epithelium is removed, the preparations instead display a strong, smooth type of tone.

In short, the animal experiments in said thesis showed that the spontaneous tone to a large degree is controlled by powerful regulating factors released from neuroepithelial endocrine (NEE) cells.

Later experiments, not included in the thesis, have revealed that one of the regulating factors is serotonin, also called 5-HT, which exerts agonist action on the receptors 5-HT_1, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 as well as on 5-HT_2 receptors.

Additional experiments have shown that when 1 µM serotonin was added to denuded airway smooth muscle preparations from the guinea-pig displaying a strong, smooth

spontaneous tone, the average force level was increased significantly, *i.e.* a contraction was observed. A contractile effect of serotonin on airway smooth muscle has been reported in *e.g.* Skogvall, S., Korsgren, M., Grampp, W., *J. Appl. Phys.*, 86:789-798, 1999. However, when 10 µM of serotonin was added, the spontaneous tone was significantly suppressed to a level of about half the force observed in control (drug-free) conditions. The spontaneous tone returned to approximately its normal level when the preparations were again exposed to control conditions. Thus, it has now surprisingly been shown that serotonin brings about contraction of the airways at low concentrations and relaxation at high concentrations, consequently having a dual effect on the airways.

Furthermore, it has been shown that when the contracting 5-HT_{2a} receptor was blocked with ketanserin, the 5-HT, i.e. serotonin, induced almost no contraction, but instead only a significant relaxation. Similar experiments have also been performed on human in vitro preparations, from patients undergoing lobecotomy or pulmectomy due to lung cancer. It was found that in this tissue, 5-HT was even more potent in relaxing the airway smooth muscle than in guinea pig. In human tissue, already 1 µM 5-HT induces a significant relaxation of the spontaneous tone.

Human airways are generally considered to display only a weak contraction when exposed to 5-HT. Nevertheless, examinations on spontaneous tone on human in vitro preparations have shown that 5-HT indeed has a contractile component also in this tissue. However, this contraction takes a longer time to develop than in guinea pig and the contractile effect is seen as a termination of the relaxation, rather than an increase of tone from the baseline. In guinea pig trachea, the contraction reaches a maximum after approximately 10 min, and this is followed by a considerable reduction of tone. However, human preparations instead induce a maximum relaxing ef-

fect after 5-10 min, which disappears gradually during the following 30-45 min (see Fig 1). The transient nature of the 5-HT relaxation is most likely caused by a simultaneous activation of the fast, relaxing 5-HT_4 receptor, and a slower activation of the contracting 5HT_{2a} receptor. This is clear, because activation of the relaxing 5-HT_4 receptor by a substance that lacks 5-HT_{2a} receptor activating properties (such as 5-carboxiamidotryptamine or SC 53116), results in a relaxation that is persistent and not transient (see Fig. 1).

It has previously been suggested that 5-HT or 5-HT analogues may be useful in the treatment of bronchoobstructive diseases. In SU 1 701 320 it is suggested that the 5-HT, i.e. serotonin, may be of use as an addition to standard beta2 receptor stimulation. However, from our experiments it seems clear that 5-HT is not effective or useful as the only treatment for e.g. asthmatic disorders, because of the transient relaxing effect by 5-HT (see Fig. 1). If instead, as we propose herein, a 5-HT analogue that lacks the 5-HT_{2a} activating properties is given, the relaxing effect is persistent, and not transient.

In summary, it has now been discovered that agonist action on the 5-HT_4 receptor results in a relaxing effect, whereas agonist action on 5-HT_{2a} receptors results in a contractile effect. In conclusion, the dual effect of serotonin is most likely a result of its agonist action on the relaxing 5-HT_4 receptor as well as on the contracting 5-HT_{2a} receptor.

It was also deduced from these experiments that compounds having agonist activity to the 5-HT_4 receptor, while having only low or no agonist activity to a 5-HT_{2a} receptor, therefore are useful as agents for treatment of bronchocontraction disorders.

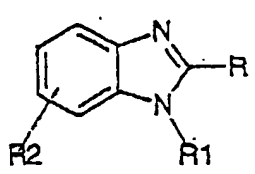
Thus, the present invention relates to the use of compounds having agonist activity to the 5-HT_4 receptor in the manufacture of a medicament intended for treatment

of bronchocontraction disorders, whereby said compounds have the strong bronchorelaxing effect of serotonin but have substantially no contractile effect. As mentioned above, the compounds used according to the present invention have only low or no agonist activity to 5-HT_{2a} receptors.

In the above mentioned experiments it has also been shown that compounds having antagonist activity to a 5-HT_{2a} receptor are useful as agents for treatment of bronchocontraction disorders, since they are capable of blocking the contractile effect of a compound having agonist activity to a 5-HT_{2a} receptor. The compounds according to the present invention having antagonist activity to the 5-HT_{2a} receptor may even be administered together with serotonin in the form of a complement to the serotonin content already present in the body with a view to obtaining an amplified contracting effect; or with any other substance having agonist activity to the 5-HT_{2a} receptor; or with a serotonin uptake inhibitor.

Said administration can be simultaneous or sequential, and a powerful relaxing effect on the bronchi can be achieved in this manner. Thus, the present invention also relates to the combined use of a compound having antagonist activity to a 5-HT_{2a}-receptor and a compound having agonist activity to the 5-HT_4 receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction.

Further 5-HT4 agonist structures useful according to the present invention



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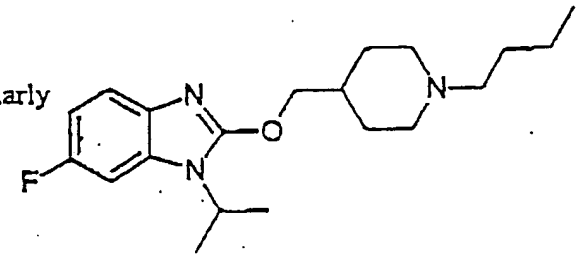
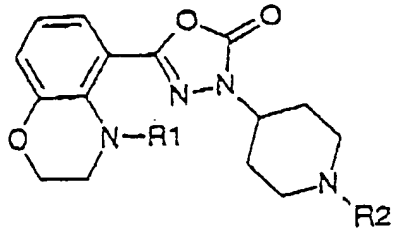


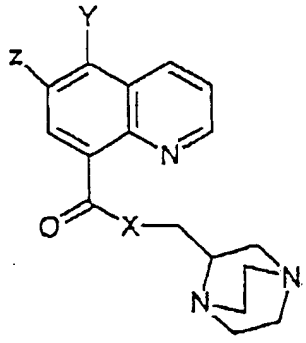


Arylcarbamate derivatives of 1-piperidineethanol
4-amino-5-chloro-2methoxybenzoic acid esters,

e.g. ML10302, RS 57639 and SR59768

4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide,e.g. TKS159

thiophene carboxamide derivatives 3 (a-j)
5. Azabicyclo(x.y.z) derivatives
2-piperazinylbenzoxazole derivatives
2-piperazinylbenzothiazole derivatives, e.g. VB20B7
clebopride
Sandoz compound 1b



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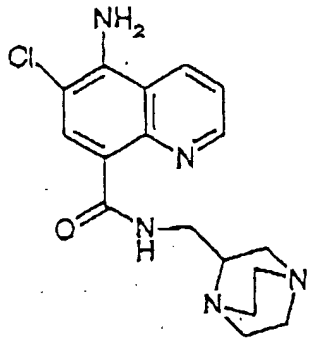

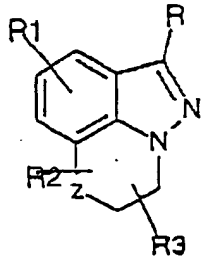

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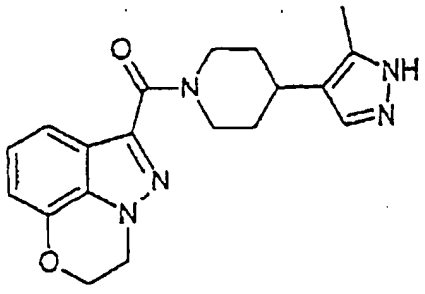

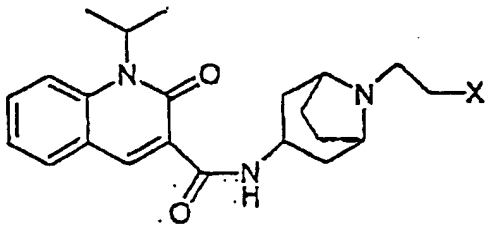

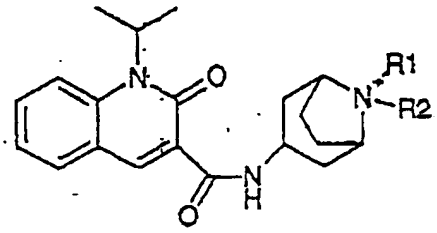

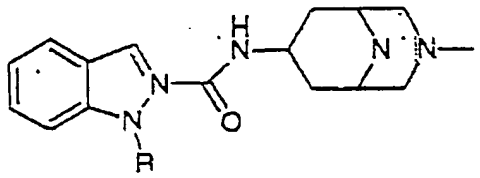

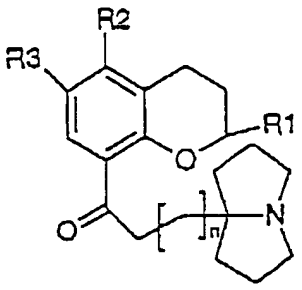

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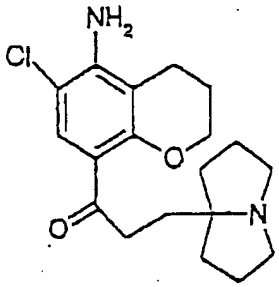
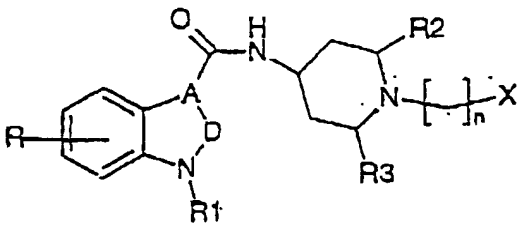
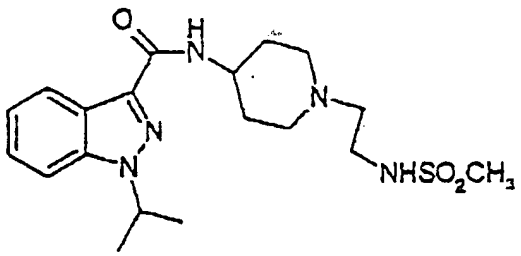
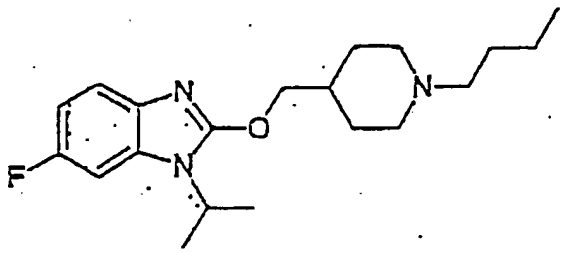


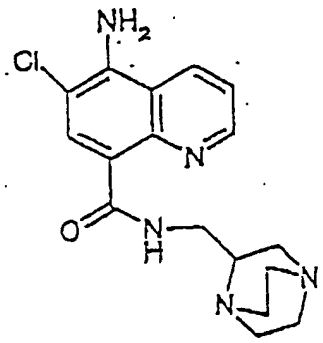


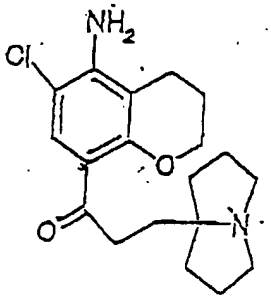


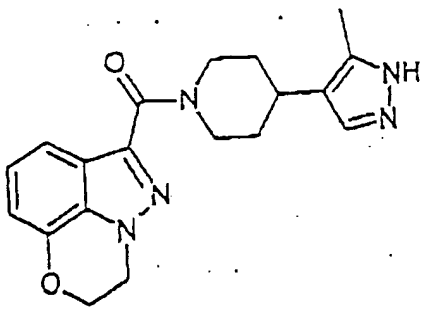
CLAIMS

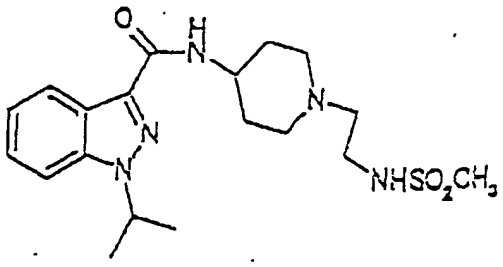
1. Use of one or more compounds having agonist activity to a 5-HT_4 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving human bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said compounds have the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compounds are chosen from the group comprising 5-carboxamidotryptamine, BIMU 1, BIMU 8, BRL 24924, Cisapride, DAU 6236, 5-hydroxy-N,N-dimetyltryptamin, ML-1035, ML 10302, 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877, Renzapride, RS 17017, RS 56532, RS 57639, RS 67333, RS 67506, RS 67532, SB 204070, SB 205149, SC-53116, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, YM-47813, YM-53389, YM-09151, Zacopride, Zelmac, arylcarbamate derivatives of 1-piperidineethanol, 2-piperazinylbenzoxazole derivatives, clebopride, and











and derivatives and pharmaceutically acceptable salts thereof,

2. Use according to claim 1, wherein said compound is VB20B7, RS 67333, BIMU 1, BIMU 8, 5-methoxytryptamine, Zacopride, RS 56532, Mosapride, BRL 24924, or SC-53116.

3. Use according to any one of the previous claims, wherein said disorder involving bronchocontraction is asthma and disorders related thereto.

4. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient, suffering from asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, a therapeutically effective amount of a compound according to any one of claims 1 and 2.

5. Use of one or more compounds having antagonist activity to a 5-HT_{2a} receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT_{2a} receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving human bronchocontraction chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease.

6. Use according to claim 5, wherein said compounds have the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compounds are chosen from the group comprising AMI-193 and MDL 100,907, ALEPH-2, Amperozide, amesergide, aryloxyalkylimidazolines, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-6-fluoroindolin-2(1 H)-one, CGS 18102A, Cyproheptadine, Deramciclane, Desmethyl-WAY 100635, dotarizine, DV 7028, Elymoclavine, Fananserin, 8-[3-(4-fluorobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, FG5893 hydrochloride, FG5974, FG5983, hexahydrocarbazoles, (3H)WAY

100635, ICI 169,369, 8-[3-(4-iodobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, LEK-8804, LSD, LU 111995, (S,S)-LY-53,857, (R,S)-LY-53,857, (S,R)-LY-53,857, (R,R)-LY-53,857, LY-53,857 free base, LY 215840, MDL-11,939, MDL 28133A, MDL 100,151, MDL 100,907, mesulergine, Metergoline, 1-3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl indolin-2(1H)-one, methysergide, Mianserin, NE-100, Nefazodone, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, NRA0045, Olanzapine, Ondansetron, 1-(2-pyrimidinyl)piperazine derivatives, Pizotifen, raclopride, Roxindole, Risperidone, Ritanserin, RP62203, sarpogrelate and its active metabolite (M-1), serotonin reuptake inhibitors like fluoxetine, YM 992, medifoxamine, cericlamine, imipramine, iprindole, BIMT 17, citalopram, paroxetine, sertraline, fluvoxamine spiro indoles N-substituted with a 3-(dimethylamino)propyl chain, Spiperone, SR 46349B, WAY 100635, and WY-50,324, and derivatives and pharmaceutically acceptable salts thereof.

7. Use according to claim 6, wherein said compound is AMI-193, MDL 11,939, WAY 100635, Spiperone, Pizotifen, Risperidone, Ritanserin, Fluoxetin, Fluvoxamin, or FG 5983.

8. Use according to any one of claims 5-7, wherein said disorder involving bronchocontraction is asthma and disorders related thereto.

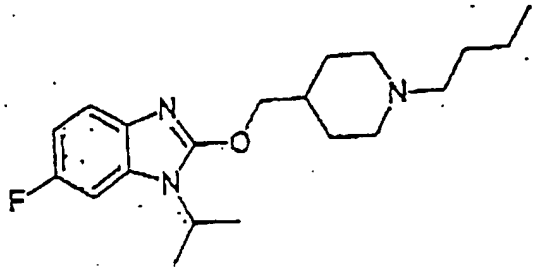
9. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient, suffering from asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, a therapeutically effective amount of a compound according to any one of claims 5-7.

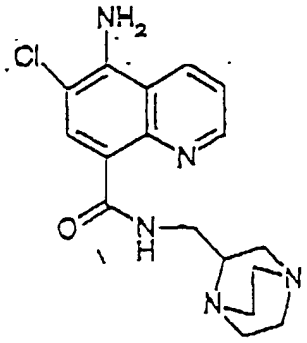
10. Use of a composition comprising a combination of at least one compound with agonist activity to the 5-HT_1 receptor, and at least one compound with antagonist activity to the 5-HT_{2a} receptor for the manufacture of a medicament for therapeutic or prophylactic treatment of

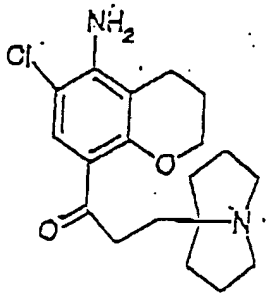
disorders involving bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, preferably asthma and disorders related thereto.

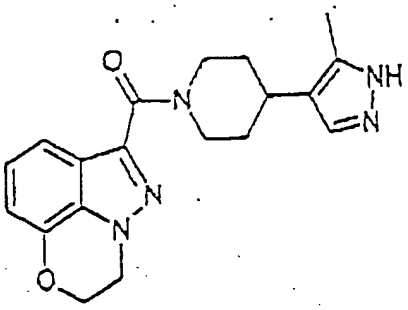
11. Use according to claim 10, wherein said composition has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said combination is chosen from the following groups of a) 5-HT_4 receptor agonists, and b) 5-HT_{2a} receptor antagonists, or derivatives or pharmaceutically acceptable salts thereof:

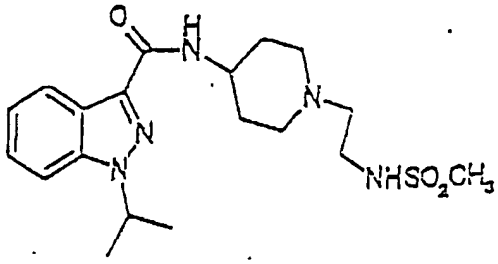
a) 5-HT_4 receptor agonists: 5-carboxamidotryptamine, BIMU 1, BIMU 8, BRL 24924, Cisapride, DAU 6236, 5-hydroxy-N,N-dimetyltryptamin, ML-1035, ML 10302, 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877, Renzapride, RS 17017, RS 56532, RS 57639, RS 67333, RS 67506, RS 67532, SB 204070, SB 205149, SC-53116, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, YM-47813, YM-53389, YM-09151, Zacopride, Zelmac, arylcarbamate derivatives of 1-piperidineethanol, 2-piperazinylbenzoxazole derivatives, clebopride, and











and serotonin (5-HT) and derivatives and pharmaceutically acceptable salts thereof.

b) 5-HT_{2a} receptor antagonists: AMI-193 and MDL 100,907, ALEPH-2, Amperozide, amesergide, aryloxyalkylimidazolines, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-6-fluoroindolin-2(1 H)-one, CGS 18102A, Cyproheptadine, Deramciclane, Desmethyl-WAY 100635, dotarizine, DV 7028, Elymoclavine, Fananserin, 8-[3-(4-fluorobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, FG5893 hydrochloride, FG5974, FG5983, hexahydrocarbazoles, (3H)WAY 100635, ICI 169,369, 8-[3-(4-iodobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, Ketanserin, LEK-8804, LSD, LU 111995, (S,S)-LY-53,857, (R,S)-LY-53,857, (S,R)-LY-53,857, (R,R)-LY-53,857, LY-53,857 free base, LY 215840, MDL-11,939, MDL 28133A, MDL 100,151, MDL 100,907, mesulergine, Metergoline, 1-3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl indolin-2(1H)-one, methysergide, Mianserin, NE-100, Nefazodone, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, NRA0045, Olanzapine, Ondansetron, 1-(2-pyrimidinyl)piperazine derivatives, Pizotifen, raclopride, Roxindole, Risperidone, Ritanserin, RP62203, sarpogrelate and its active metabolite (M-1), serotonin reuptake inhibitors like fluoxetine, YM 992, medifoxamine, cericlamine, imipramine, iprindole, BIMT 17, citalopram, paroxetine, sertraline, fluvoxamine spiro indoles N-substituted with a 3-(dimethylamino)-propyl chain, Spiperone, SR 46349B, WAY 100635, and WY-50,324, and derivatives and pharmaceutically acceptable salts thereof.

12. Use according to claim 11, wherein the composition comprises the following combinations of a 5-HT_4 receptor agonist and a 5-HT_{2a} receptor antagonist: VB20B7 and AMI-193, VB20B7 and MDL 11939, RS67333 and AMI-193, RS67333 and MDL 11939, VB20B7 and WAY 100635, RS67333 and WAY 100635, Zacopride and AMI-193, Zacopride and

MDL 11939, RS56532 and AMI-193, RS56532 and MDL 11939, VB20B7 and Fluvoxamin, RS67333 and Fluvoxamin.

13. A method for treatment of disorders involving bronchocontraction chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a composition according to any one of claims 10-12.

14. A method for treatment of disorders involving bronchocontraction chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a 5-HT_4 receptor agonist according to any one of claims 1 and 2 and a 5-HT_{2a} receptor antagonist according to any one of claims 5-7, either simultaneously or sequentially.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00819

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/395
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5418241 A (SAMIR JEGHAM ET AL), 23 May 1995 (23.05.95)	
A	WO 9717345 A1 (SYNTHELABO), 15 May 1997 (15.05.97)	
A	STN, International, File CA, Chemical Abstracts, volume 117, no. 7, 17 August 1992 (Columbus, Ohio, US), Taivan, I.L. et al: "Method for stopping bronchial asthma attack"; & 63015, SU,A1,1701320, 19911230	

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 2000	29 -08- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/ELY Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00819

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7,16
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. ☒ Claims Nos.: 1-6,8-15,17
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See extra sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00819

The claims are of a plurality of different categories and contain a plurality of alternatives and parameters which render it difficult, if not impossible to determine the matter for which protection is sought. The present application therefore fails to comply with the clarity and conciseness requirements of Article 6 PCT to such an extent that a meaningful search on the basis of the claims is impossible.

Expressions such as "compound ... having agonist activity to a 5-HT4 receptor" are unclear and defined in terms of the result to be achieved. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. Further, expressons such as "disorders involving bronchocontraction" and "derivatives" are not clear and concise.

Due to the complexity of the claims, a search has been carried out for those parts of the claims which appear to be supported and disclosed, namely the part of claim 4 which refers to claim 2. The search has been aimed at documents having explicit information of use for treatment of bronchocontraction.

The applicants attention is drawn to the fact that claims relating to inventions in which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE 00/00819

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5418241 A	23/05/95	AU	659033 B	04/05/95
		AU	4860593 A	14/04/94
		CA	2107060 A	29/03/94
		CN	1087340 A	01/06/94
		CZ	9302014 A	13/04/94
		EP	0591026 A	06/04/94
		FI	934220 A	29/03/94
		FR	2696176 A,B	01/04/94
		HU	65396 A	28/06/94
		HU	211490 B	28/11/95
		HU	9302726 D	00/00/00
		HU	9500434 A	28/09/95
		IL	107132 D	00/00/00
		JP	6192254 A	12/07/94
		MX	9305930 A	30/06/94
		NO	933434 A	29/03/94
		NZ	248775 A	24/02/95
		PL	172852 B	31/12/97
		PL	300514 A	05/04/94
		SK	103293 A	10/08/94
		ZA	9307155 A	23/05/94
WO 9717345 A1	15/05/97	AT	181328 T	15/07/99
		AU	707325 B	08/07/99
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		BG	102412 A	31/08/99
		BR	9611311 A	29/06/99
		CA	2236357 A	15/05/97
		CN	1202169 A	16/12/98
		CZ	9801421 A	12/08/98
		DE	69602970 D	00/00/00
		EP	0863897 A,B	16/09/98
		SE	0863897 T3	
		FR	2741069 A,B	16/05/97
		IL	124364 D	00/00/00
		NO	982092 A	29/06/98
		NZ	321626 A	28/10/98
		PL	326671 A	12/10/98
		SK	59998 A	04/11/98
		US	5929089 A	27/07/99
		FR	2741070 A,B	16/05/97
		FR	2745574 A,B	05/09/97